IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: William J. Curatolo et al.

SERIAL NO.: 09/770,562

FILED: January 26, 2001

FOR: Solid Pharmaceutical Dispersions with Enhanced Bioavailability

Examiner: B. Fubara
Art Unit: 1618

Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.131

I, James A.S. Nightingale, declare that:

1. I was awarded the degree of Bachelor of Science in Chemical Engineering in 1980 by the University of Washington, Seattle, Washington, a degree of Master of Science in 1986 in Bioengineering by the University of Washington, Seattle, Washington, and a Ph.D. in 1988 in Bioengineering by the University of Washington, Seattle, Washington.

2. Prior to being employed with Bend Research I was employed from 1988-1993 as a Staff Scientist by Ciba-Geigy Corporation, Pharmaceuticals Division, Ardsley, New York where my areas of expertise included transdermal drug-delivery research and the development of second-generation transdermal pharmaceutical products; and from 1980-1988 as a Research Assistant for the University of Washington, Seattle, Washington, where my areas of emphasis included biomaterials, polymer synthesis and characterization, organic chemistry, biochemistry, and chemical engineering.

3. I have been employed by Bend Research, Inc., of which I am also a part owner since 1993. My title is Director, Pharmaceutical Research.

4. Bend Research, Inc. is part-owned by Pfizer, Inc., the Assignee of the above-identified application.

5. I am an inventor of the instant patent application.

6. I have reviewed the examples in the instant application. In particular attached to this declaration as Exhibit A are notebook pages relating to work I supervised in connection with the process used to form solid amorphous dispersions of a drug and hydroxypropylmethyl cellulose acetate succinate (or HPMCAS), as well as Examples 25 and 26 of the instant application. The notebook pages show that drugs were spray dried with HPMCAS to form solid amorphous dispersions. The dates on the notebook pages have been redacted. However, these examples were made prior to February 13, 1997.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true; and further that these statements were made with the knowledge that willful false statements and the likes made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

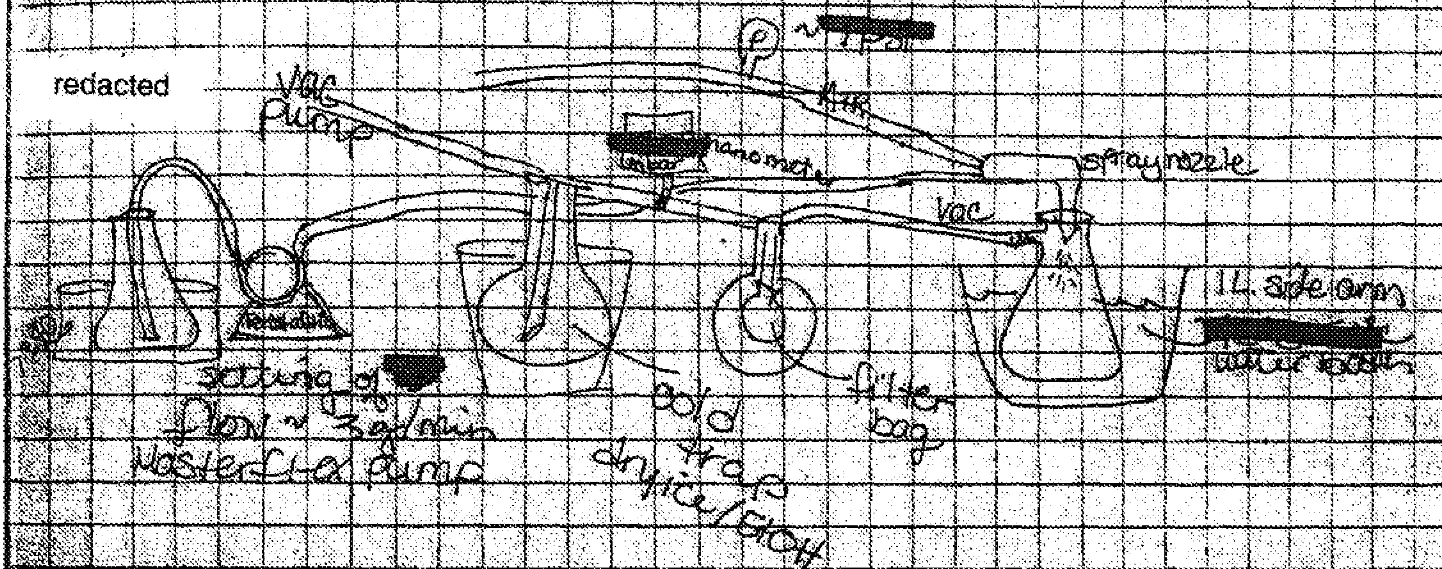
24 May 2007

Date

James A.S. Nightingale

G:\BRI Corporate\legal\Patent\PC 9674 HPMCAS SDDs\JASN Declaration 3-1-07.doc

From Page No. Making spray-dried solvent dispersion.
This is the set-up



filter bag - paper towel rubber-banded to the inner part of the trap

Masterflex pump - head 7013-20
tubing 6404-14

Make disp of CP 143867 / HPMCAS - see pg 15 for results

[redacted]

Witnessed & Understood by me, | Date redacted | Invented by | Date redacted
Recorded by Chris Hostetler

Project No.______

TITLE______ Book No.______ 77

From Page No. Gris/HPMCAS spray-dried disp (1:10)
9

1800mg HPMCAS 200ml Acetone
200mg Gris. 38°C
Heated Acetone, added HPMCAS when no clumps, added Griseofulvin

T0 = 3:20pm redacted H2O=45-55°C
TOC = 440mbar pump setting = 3 (~3ml/min.)
air pressure = 10psi
End @4:20pm
Tested @ Day 1 - Data on pg 1330-83 Looks good!

To Page No.______

Witnessed & Understood by me,	Date	Invented by	Date
Gail E. Bailie	redacted	Recorded by Christy Hetteler	redacted

Project No.

TITLE ______ Book No. 1330

From Page No.

See 1330-79

Griseofulvin 1:2 & 1:5 Dispersions, D1 after vacuum drying overnight.

For 1:2 ⇒ 4.01mg /10ml ⇒ 200 µg/ml
1:5 ⇒ 10.02mg /10 ml ⇒ 200 µg/ml

		Griseofulvin crystallization inhibition exp				Sheet1	Date:	redacted			
		Dissolution Testing					BRI Ref.:	1330-83			
							Analyst:	CL Hostetler			
RECEPTOR SOLUTION: 10ml of (50% NaTC/POPC)-H2O, pH 6.5,											
DRUG:Griseofulvin/HPMCAS spray-dried Dispersion											
Theoretical max. concentration: 200µg/ml											
Dissolution of (1:10) 10% Gris/90% HPMCAS spray-dried dispersion, Day 1											
HPLC ANALYSIS						Standard Factor:					
C18 column (Phenomenex, Ultracarb)			1ml/min								
50/50: 0.02M KH_2PO_4, pH3.0/ACN						Y-INT:	11.47584137	SLOPE:	17.3269123		
A:	Flask-1			B:	Flask-2			C:	Flask-3		
min	area	PPM	auc	min	area	PPM	auc	min	area	PPM	auc
0	0	0	0	0	0	0	0	0	0	0	0
0.5	827.47	94.1881?1	25.5470303	0.5	695.07	79.020964	19.76524101	0.5	654.98	74.1557113	18.5484278
5	1485.17	171.258878	620.803005	5	1441.47	166.060529	566.9358005	5	1458.04	168.742808	560.634486
30	1521.65	174.913488	4940.48364	30	1637.35	187.670448	4978.075751	30	1676.68	192.210202	5047.64081
60	1518.15	174.525827	10185.6203	60	1498.37	171.628347	10367.5578	60	1567.29	179.583601	10634.4479
120	1544.03	178.58875	20693.3909	120	1459.18	168.412184	20606.7725	120	1260.29	144.747387	20336.3778
180	1582.57	177.578593	31236.7805	180	1620.33	185.705589	31072.91808	180	1481.01	169.524827	29749.5385
1200	1022.84	116.789187	181692.471	1200	1616.75	180.864427	202621.168	1200	1009.2	115.184738	174962.081
D:	Filter-1			E:	Filter-2			F:	Filter-3		
min	area	PPM	auc	min	area	PPM	auc	min	area	PPM	auc
0	0	0	0	0	0	0	0	0	0	0	0
0.5	898.72	101.639186	25.4567961	0.5	710.48	80.5864286	20.17135669	0.5	789.18	89.7584069	22.4421017
5	1626.23	165.682271	622.68557	5	1474.89	169.818512	581.7793185	5	1324.39	151.646282	585.400174
30	1457.35	168.893616	4752.8579	30	1550.89	177.702185	4914.93806	30	1612.24	178.228324	4825.09538
60	1493.78	171.098855	9822.73665	60	1524.98	174.699509	10200.56246	60	1471.77	168.557978	9751.90492
120	1423.62	163.023238	19846.3918	120	1502.34	172.080593	20604.18659	120	1425.37	163.271405	19706.7664
180	1498.06	171.59141	29894.8311	180	1495.58	171.01869	30897.32063	180	1439.38	164.619286	29549.5071
1200	807.03	91.8287855	184229.131	1200	1120.81	128.05913	183427.111	1200	1185.08	135.468104	187695.098

Data was overwritten by 1:2 data, ... 1:10 data is ... made on 1330-77

0 30 60 90 120 150 180

Time (min)

—◆— flask-1 —■— flask-2 —▲— flask-3 —×— filter-1 —✱— filter-2

To Page No.

Witnessed & Understood by me,	Date	Invented by	Date
(signature)	redacted	Recorded by (signature)	redacted

Project No.____
TITLE ____ Book No. 1330

From Page No.____

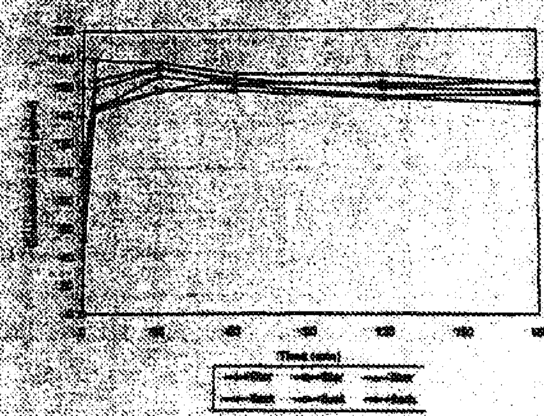
500mg Gris 2250ml
20g HPMCAS / Acetone

1:4 Griseofulvin/HPMCAS

Time	min	air	vac	H2O	Acetone	pump
1/27 3:50	Ø	11	352	53°C	45°C	25
4:15	25	11	354	55°C	44°C	25
4:40	50	11	333	54°C	39°C	25
5:00	70	11	300	55°C	38°C	25

end - when I came back in the room & checked on the spray, the filter must have been plugged because the spray nozzle stop had "popped" & wasn't sealing, but the vacuum was still reading 300mbar. There wasn't much liquid left to spray, so I turned off the feed pump & let the dispersion dry as much as possible. When recovering the dispersion - it looked OK - not wet, & I still vacuum-dried it overnight anyway.

Type of Experiment [illegible]
Drug [illegible]
Receptor Solution [illegible]
Date Performed redacted
Operator CLH
Notebook 1330-97
Comments [illegible]



To Page No.____

Witnessed & Understood by me, [signature] | Date redacted | Invented by | Date redacted
Recorded by [signature]